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PATENT APPLICATION TRANSMITTAL LETTER

Date: June 30, 2000

In re: Application of Michael F. Murray, M.D.

Serial No.: Not Yet Assigned

Filed: Concurrently

Title: Treatment of Retrovirus Induced Derangements With Niacin Compounds

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- ☒ Fee Transmittal Form
- ☒ Eighteen (18) pages of patent application
- ☒ Four (4) Sheets of Drawings
- ☒ Signed Declaration and Power of Attorney
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Application or Patent No.: _____
Filed or Issued: _____
Title: TREATMENT OF RETROVIRUS INDUCED DERANGEMENTS WITH NIACIN COMPOUNDS

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NAME OF PERSON SIGNING MICHAEL F. MURRAY, M.D.

TITLE IN ORGANIZATION OF PERSON SIGNING PRESIDENT

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Treatment Of Retrovirus Induced Derangements With Niacin Compounds

FIELD OF INVENTION

This invention relates to the treatment of mammals chronically infected with retroviruses, such as human immunodeficiency virus [HIV].

BACKGROUND

Retroviruses lead to chronic infection in mammals. Retroviruses are packets of infectious nucleic acids (i.e. genetic material) surrounded by a protective protein coat. Retroviruses are incapable of generating metabolic energy or synthesizing proteins, and thus are characterized by dependence on living cells for replication and proliferation. A retrovirus contains three enzymes: (1) reverse transcriptase, (2) protease, and (3) integrase. Current antiviral drug therapy focuses on the inhibition of reverse transcriptase and protease enzymes.

HIV is a prototypic retrovirus that causes the acquired immunodeficiency syndrome [AIDS] in humans and related primates. Worldwide, AIDS has claimed over 11 million lives. HIV currently infects more than 30 million people. Since the first reported cases of AIDS almost 20 years ago, the medical community has learned much about this retroviral disease and its diverse manifestations. A number of clinical

manifestations of HIV infection, however, remain unexplained despite the efforts of the medical community to discover their etiology.

The Center for Disease Control and Prevention (the "CDC") has developed a "case definition" of the specific findings which, if present in a person with HIV, define AIDS. *See* Center for Disease Control and Prevention, *1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults,* MMWR Morb Mortal Wkly Rep, 41(RR-17): 1-19(1992). The CDC's case definition falls into three broad categories: (1) CD4 immune cell depletion, (2) opportunistic infections, and (3) malignancies.

In addition to the case definition of AIDS, a number of metabolic changes are associated with this chronic infection. Among them are alterations in the circulating concentrations of amino acids. Amino acids are often referred to as the building blocks of proteins. Of the common amino acids, ten amino acids are "essential." The essential amino acids are those which the body cannot synthesize and therefore must be obtained directly through the diet.

Tryptophan, an essential amino acid, is known to be depleted during HIV infection. The body utilizes dietary-derived tryptophan for several important biochemical functions, including: (1) as a building block in the synthesis of proteins, (2) as a precursor of niacin and nicotinamide adenine dinucleotide [NAD], and (3) as a precursor of serotonin. Attempting to simply replete plasma tryptophan directly through pharmacologic doses of tryptophan is not advisable given the history of patients developing "eosinophillia myalgia syndrome."

Chronic retroviral infections lead to an ongoing metabolic burden on the infected subject. This burden in HIV infection includes: (1) the turnover of CD4 cells, (2) the disturbance of lipid metabolism, (3) the depletion of serotonin, (4) the depletion of plasma tryptophan [as discussed above], and (5) the depletion of intracellular NAD. The infection, over the course of months, leads to immunodeficiency (marked by CD4 depletion) and opportunistic infections. The infection also leads to a metabolic disease state marked by a number of other manifestations, including a non-specific "wasting syndrome" and the specific disturbances and depletions previously mentioned in this paragraph.

Presently, no cure exists for HIV infection. Current treatments for HIV infected patients tend to focus on agents which inhibit two viral enzymes: the HIV-reverse transcriptase [reverse transcriptase inhibitors] or the HIV-protease [protease inhibitors]. Such agents include among others, ZDV (zidovudine), DDI (2'-3' -dideoxyinosine), and DDC (2' -3' -dideoxycytidine), each of which blocks the HIV proliferation in cells (ZDV, DDI , DDC and other such agents are referred to as the "licensed antivirals"). Unfortunately, the inhibition which occurs with the licensed antivirals is incomplete. Over time, HIV becomes resistant to the licensed antivirals. This resistance can result in a resumption of progressive immune system destruction.

Zidovudine, a licensed antiviral compound, is the only compound known to replete plasma tryptophan in HIV infected persons. However, zidovudine which is a reverse transcriptase inhibitor, causes a number of side effects including headache, nausea, and bone marrow suppression. Furthermore, HIV can develop resistance to

Zidovudine, an event which would be expected to result in recurrent tryptophan depletion.

Since HIV depletes plasma tryptophan and since this essential amino acid is required in a range of biologically necessary tasks, replenishing plasma tryptophan is essential in maintaining overall health in the HIV infected state. Although the antiviral drug zidovudine leads to an increase in plasma tryptophan in HIV infected persons, this reversal would be expected to last only so long as virus inhibition persists, and antiviral drug failure is expected with time given the incomplete nature of the drug's inhibitory effect. Niacin, as an agent to reverse infection-induced metabolic changes, works on the host side of the virus-host interaction and therefore would not be subject to the same risk of eventual viral drug resistance.

BRIEF SUMMARY OF THE INVENTION

This invention inhibits adverse metabolic and immunologic effects associated with chronic retroviral infections such as HIV by using niacin compounds, such as nicotinamide or nicotinic acid, to inhibit the depletion of tryptophan and to induce the restoration of intracellular nicotinamide nucleotides, such as nicotinamide adenine dinucleotide [NAD], in patients with retroviral infections.

More particularly, this invention relates to the oral use of pharmacologic doses of niacin compounds in persons with HIV infection in order to reverse or prevent deleterious metabolic consequences of the infection.

Another object of the invention is to inhibit adverse effects of HIV infection by combining the method of this invention with known HIV inhibitors, such as reverse transcriptase inhibitors, protease inhibitors, and others.

The invention provides a method of administering a therapeutically effective amount of niacin compounds to a patient with a chronic retroviral infection such as HIV, the etiological agent clinically associated with AIDS.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

Table 1 - Baseline Characteristics of Niacin Study Patients. Illustrates the immunological status as measured by CD4 count, the concomitant use of antiviral medications, and the presence of co-infections. Niacin worked to improve tryptophan status in all four patients across this range of baseline infectious disease related findings.

Table 2 - Baseline Dietary intake of Niacin Study Patients. Illustrates the range of baseline dietary intake of tryptophan and niacin compounds. The amounts were determined by dietary recall survey, and demonstrate that tryptophan and niacin were not deficient in the baseline diet of these patients, and that the pharmacological dose of niacin used in the study was significantly higher than all participant's baseline intake.

Table 3 - Changes in plasma tryptophan levels [micromols/l] in patients taking 3 gram of nicotinamide daily for 2 months. The increase in the levels of this essential amino acid despite the unchanged dietary intake of tryptophan is consistent with decreased metabolic shunting of essential tryptophan towards niacin in HIV infected persons.

Table 4 - Changes in non-tryptophan plasma amino acid levels in HIV patients taking 3 grams/day of oral nicotinamide. The four amino acids include two essential amino acids [methionine and lysine] and two nonessential amino acids [cysteine and taurine]. In all four cases there is no discernible pattern of change with this intervention, supporting the observation that the effect of pharmacological doses of niacin on plasma tryptophan is a specific and important intervention against the metabolic disruption caused by HIV infection.

DESCRIPTION

The invention is a method for treatment of HIV infected persons with niacin administered in an amount effective to combat plasma tryptophan depletion. This invention is useful for any mammal infected with a retrovirus, including HIV. Through administration of a pharmacological dose of niacin, the retrovirus-infected subject's systemic tryptophan depletion will be reversed.

Niacin refers to either of two chemically related compounds: nicotinamide or nicotinic acid. Niacin may be administered orally, parenterally, rectally, or with any pharmaceutically accepted adjuvant or carrier. The administration and effects of niacin have undergone extensive study in the fields of diabetes and hypercholesterolemia. (*See, e.g.,* Petley A, *et al, The Pharmacokinetics of Nicotinamide in Humans and Rodents, Diabetes*, 44: 152-155 (1995); and DiPalma JR and Thayer WS, *Use of Niacin as a Drug*, Annu. Rev. Nutr., 11:169-87, (1991)). Niacin, or vitamin B3, is the common name for both nicotinic acid, i.e., C6H5N02, (pyridine-3-carboxcylic acid) or nicotinamide, i.e., C6H6ON2 (3-10 pyridinecarboxamide).

Niacin is a precursor to the biosynthesis of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). Nicotinamide nucleotides (NAD and NADP) participate in a wide array of oxidation-reduction reactions catalyzed by dehydrogenase or oxido-reductase enzymes. Virtually every aspect of cellular metabolism involves NAD/NADH or NADP/NADPH dependent reactions. In absence of sufficient supplies of nicotinamide nucleotides or niacin precursors for nicotinamide nucleotide biosynthesis, cellular functions and life itself would be impaired. (DiPalma JR and Thayer WS, *Use of Niacin as a Drug*, Annu. Rev. Nutr., 11:169-87, (1991)). The body can readily convert nicotinic acid to nicotinamide and both are expected to produce the desired therapeutic effect of combating plasma tryptophan depletion.

For this invention, it is preferred to administer niacin in "pharmacologic doses." A vitamin compound is considered a "drug," not a "nutrient," when: [1] the ingested dose exceeds the dose required for nutrient function, and [2] a pharmacologic action distinct from nutrient function is achieved. Maintaining plasma tryptophan is not a nutrient function of niacin; rather, it is a pharmacological action of niacin in retrovirally infected subjects.

All vitamins fill a nutrient function whereby a sufficient amount of the vitamin compound is required in the diet to fulfill normal metabolic needs. The body normally requires 12-18 milligrams of niacin per day to carry out the coenzyme function which defines niacin as a vitamin. The Recommended Daily Allowance [RDA] of niacin is approximately 13-20 milligrams per day. Therefore, a non-pharmacologic dose of niacin,

where niacin acts as a vitamin or nutrient compound, is approximately 20 milligrams a day or less.

The use of pharmacologic doses of niacin is distinct from the vitamin or nutrient use of niacin. (DiPalma JR and Thayer WS, *Use of Niacin as a Drug*, Annu. Rev. Nutr., 11:169-87, (1991)). Niacin's pharmacologic use can be distinguished from its non-pharmacologic (or physiologic) use by the pharmacodynamic action of the compound. Pharmacodynamic action begins when the nutrient function of niacin is complete. The maintenance of plasma tryptophan in the face of (1) retrovirus infection, and (2) normal or supernormal niacin levels is the distinct pharmacodynamic action described here.

A pharmacological dose of niacin generally occurs at a dose of about 100 milligrams per day, about 5 times the recommended daily allowance [RDA]. Niacin is safe in doses greater than 100 mg in persons with HIV, and doses of greater than 100 mg should also cause a retrovirus-infected patient to undergo a reverse systemic tryptophan depletion.

Because pharmacologic doses of niacin alleviate the drive to deplete plasma tryptophan, tryptophan depletion may represent a metabolic shunt towards niacin production. (*See* Murray, *Niacin as a Potential AIDS Preventative Factor*, Medical Hypotheses 53(5), 375-379 (November 1999), which is incorporated herein by reference.) In addition, because the essential amino acid tryptophan cannot be synthesized in the body, any agent which increases in the circulating concentrations of tryptophan in HIV infected persons presumably does so by diminishing the metabolic demands on the available supply.

The preferred embodiment of this invention is to administer a mammal infected with a retrovirus with niacin. The preferred method of administration is oral administration. The preferred dose is 500 milligrams of niacin per day in the form of nicotinamide.

The following EXAMPLE is presented to more fully illustrate the preferred embodiment of the invention. The example should not be construed to limit the scope of the invention and is to be understood merely for the purpose of illustration.

EXAMPLE - Clinical Trial of Niacin in HIV infected persons.

Four HIV infected persons participated in a trial of niacin in the form of nicotinamide. The participants were at various stages of their HIV infection as judged by their CD4 counts which ranged from 0 to 620 [see table 1]. The participants were receiving either a stable regimen of anti-viral drugs [i.e. anti-HIV drugs] for a period greater than one year or were not taking any anti-viral drugs. Two of the participants had known co-infections infections typical of HIV infected persons. Each participant took 3 grams of nicotinamide per day for 2 months. This treatment was not associated with any adverse side effects. Each participant's plasma tryptophan was measured prior to treatment and at the end of treatment [see table 3]. The average increase of plasma tryptophan of all participants was 43.9%. This change in tryptophan concentration was statistically significant with a calculated p value of p=0.0112 [using paired t-test]. The study also measured 4 other plasma amino acids which are listed in table 4. All amino acid concentrations were measured by High Performance Liquid Chromotography [HPLC]. There was no significant change in the plasma amino

acid concentrations other than tryptophan. As demonstrated in tables 3 and 4, only plasma tryptophan changed in a statistically significant manner.

The details of the invention have been set forth in the accompanying description and example above. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials have been described. Other features, object, and advantages of the invention will be apparent from the description and from the claims. In the specification and the claims, the singular forms include plural referents unless the context clearly requires otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All patents and publications cited in this specification are incorporated by reference.

CLAIMS

What is claimed is:

1. A method for treating a patient infected with a retrovirus, which comprises the step of administering a daily pharmacological dose of niacin.

2. A method for treating retrovirus-induced metabolic changes, which comprises the step of administering a daily pharmacological dose of niacin.

3. A method for treating a patient infected with HIV, which comprises the step of administering a daily pharmacological dose of niacin.

4. A method for treating HIV-induced metabolic changes, which comprises the step of administering a daily pharmacological dose of niacin.

5. A method for treating retrovirus-induced metabolic changes in a patient's systemic tryptophan levels, which comprises the step of administering a daily pharmacological dose of niacin.

6. A method for treating HIV-induced metabolic changes in a patient's systemic tryptophan levels, which comprises the step of administering a daily pharmacological dose of niacin.

7. A method for treating the depletion of tryptophan in a retrovirus-infected patient, which comprises the step of administering a daily pharmacological dose of niacin.

8. A method for treating the depletion of tryptophan in an HIV-infected patient, which comprises the step of administering a daily pharmacological dose of niacin.

9. A method for repleting nicotinamide nucleotide precursors, which comprises the step of administering a daily pharmacological dose of niacin.

10. The method of claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose is of an amount sufficient to prevent retrovirus-induced metabolic changes in systemic tryptophan concentrations.

11. The method of claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose is of an amount sufficient to slow down the rate of retrovirus-induced metabolic changes in systemic tryptophan concentrations.

12. The method of claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose is of an amount sufficient to stop the rate of retrovirus-induced metabolic changes in systemic tryptophan concentrations.

13. The method of claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose is of an amount sufficient to increase a patient's level of plasma tryptophan.

14. A method as in claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose is greater than 100 milligrams per day.

15. A method as in claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose is approximately 3 grams per day.

16. A method as in claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose exceeds the standard recommended daily amounts for coenzyme activity.

17. A method of claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose exceeds amounts normally obtainable with routine diet and supplement practices.

18. A method as in claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose exceeds the RDA [recommended daily allowance] of niacin.

19. A method as in claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose is sufficient to raise the intracellular levels of nicotinamide adenine dinucleotide [NAD] in persons with HIV infection.

20. A method as in claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose is sufficient to replete nicotinamide nucleotide precursors [NAD].

21. A method of claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose of niacin is administered to persons with HIV and other co-infections.

22. A method as in claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose of niacin is administered in combination with antiviral medications such as reverse transcriptase inhibitors, and protease inhibitors.

23. A method as in claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose is administered in combination with other treatments for HIV infection to improve the metabolic status of an infected patient.

24. A method as in claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose is sufficient to inhibit new virus production.

ABSTRACT OF THE DISCLOSURE

Chronic infection with retroviruses, such as HIV, induce a number of metabolic derangements. The present invention relates to a method for treating retrovirus-infected subjects with niacin compounds to reverse infection induced metabolic derangements.

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DRAWINGS

Table 1 - Baseline Infectious Disease Characteristics of Nicotinamide Study Patients.

Patient	CD4 count	Antiretroviral [duration]	Co-infections
1	0	none	molluscum contagiousum
2	220	PI[1]/RTI[2] [3 years]	none
3	290	RTI [2 years]	none
4	620	none	herpes zoster

Table 2 - Baseline Dietary Characteristics of Nicotinamide Study Patients. Daily intake for tryptophan and niacin by dietary survey [i.e. these numbers reflect the total non-pharmacologic amounts included in participants food and nutritional supplements.]

Patient	Tryptophan [daily intake]	Niacin [RDA%]
1	0.89 gms	42.0 mg [210%]
2	1.44 gms	22.4 mg [112%]
3	0.66 gms	32.8 mg [164%]
4	1.05 gms	24.0 mg [120%]

[1] PI is protease inhibitor.
[2] RTI is reverse transcriptase inhibitor.

Table 3 - Changes is plasma tryptophan levels [micromols/l] in patients taking 3 gram of nicotinamide daily for 2 months.

Patient	Days of Treatment	Baseline Plasma Tryptophan	Final Plasma Tryptophan	Change in Plasma Tryptophan
1.	57	31.1	52.9	+ 70.1%
2.	61	53.4	82.3	+ 54.1 %
3.	63	62.0	75.1	+ 21.1%
4.	60	51.0	66.5	+ 30.4%

Table 4 - Changes in non-tryptophan plasma amino acid levels in HIV infected patients taking 3 grams/day of oral nicotinamide.

Patient	Days of Treatment	Baseline Plasma Methionine	Final Plasma Methionine	Change in Plasma Methionine
1.	57	19.8	18.3	- 7.6%
2.	61	15.6	17.1	+ 9.6 %
3.	63	34.3	24.4	- 28.9%
4.	60	18.3	20.4	+ 11.5%

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Patient	Days of Treatment	Baseline Plasma Lysine	Final Plasma Lysine	Change in Plasma Lysine
1.	57	218.7	111.1	- 49.2%
2.	61	97.7	141.2	+ 44.5 %
3.	63	251.8	162.7	- 34.5%
4.	60	191.8	129.1	- 32.7%

Patient	Days of Treatment	Baseline Plasma Cysteine	Final Plasma Cysteine	Change in Plasma Cysteine
1.	57	48.3	54.7	+ 13.3%
2.	61	27.0	28.8	+ 6.6 %
3.	63	35.6	39.1	+ 9.8%
4.	60	75.5	61.3	-18.8%

Table 4 (cont.)

Patient	Days of Treatment	Baseline Plasma Taurine	Final Plasma Taurine	Change in Plasma Taurine
1.	57	46.3	68.8	+ 48.6%
2.	61	76.2	87.4	+ 14.4 %
3.	63	92.1	69.7	- 24.3%
4.	60	80.6	61.6	- 23.6%

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As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

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TREATMENT OF RETROVIRUS INDUCED DERANGEMENTS WITH NIACIN COMPOUNDS

(Title of the Invention)

the specification of which
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Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
			☐	☐	☐
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I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

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DECLARATION — Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)

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Name	Registration Number	Name	Registration Number
JOSEPH R. MEANEY	45276		

☐ Additional registered practitioner(s) named on supplemental Registered Practitioner Information sheet PTO/SB/02C attached hereto.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

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☐ Additional inventors are being named on the ___ supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto

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